Scientific Abstract

This open-label, gene therapy clinical study will evaluate the safety and efficacy of repeat treatment with pVGI.1(VEGF2) plasmid deoxyribonucleic acid (DNA) in patients with critical limb ischemia (CLI) who have previously failed to improve or whose condition has worsened after treatment with pVGI.1(VEGF2) in a previous study conducted under BB-IND 7911 or BB-IND 7961. The pVGI.1(VEGF2) plasmid contains the complementary DNA sequence for the vascular endothelial growth factor 2 (VEGF-2) protein, a member of a class of natural growth factors that promote angiogenesis. This study will obtain information regarding the safety and the effectiveness of this gene for the treatment of critical limb ischemia.

The primary objectives of this study in adult patients with moderate-risk (Rutherford Clinical Severity Score equal to 4) or high-risk CLI (Rutherford Clinical Severity Score greater than or equal to 5) who have previously received pVGI.1(VEGF2) without sustained benefit are as follows:

- To evaluate the safety of one or more doses of pVGI.1(VEGF2) given at intervals of no less than 4 weeks by intramuscular injection into the affected leg by assessing the frequency, duration, and severity of adverse events

- To evaluate the effect and duration of effect of one or more doses of pVGI.1(VEGF2) given at intervals of no less than 4 weeks by intramuscular injection into the affected leg on resting leg pain (intensity and frequency), Rutherford Clinical Severity Score, and leg ulcer healing (as assessed by ulcer surface area and time to complete healing) measured before and after treatment

The secondary objective of this study is the following:

- To evaluate whether administration of one or more doses of pVGI.1(VEGF2) given at intervals no less than 4 weeks by intramuscular injection into the affected leg is an effective treatment for preventing or reducing the extent of lower leg amputation or other surgical or vascular interventions

To qualify for pVGI.1(VEGF2) treatment, the patient must not have demonstrated a sustained beneficial response to previous treatment and have a condition that has worsened from the baseline condition of the preceding study as determined by any one or more of the following observations :

- Increase in rest pain (25% increase in frequency of rest pain as recorded in the patient diary for at least one week)

- Increase in use of analgesics (25% increase in weekly pain medication usage as quantitated in morphine equivalent units for a period of at least one week)

- Increase in ulcer size (25% increase in surface area of ulcer)

- Increase in number of ulcers (appearance of 1 or more new ulcers)

- Evidence of decreased tissue perfusion in the affected limb (as assessed by skin color and turgor, magnetic resonance angiography, or angiogram)

- In the opinion of the Investigator, the results of diagnostic procedures and/or a combination of clinical signs and symptoms indicate that the patient's condition is worsening

If the patient meets requirements for treatment, the dose level of pVGI.1(VEGF2) to be administered will be equivalent to the highest single dose that has been safely administered in any clinical study conducted under BB-IND 7911 or BB-IND 7961. Up to 2 additional doses that are equivalent to the first dose may be administered at 4-week intervals, with the administration of the second and third doses dependent on the patient's response to previous doses.

An efficacy analysis will be conducted on all patients randomized into the study (*i.e.*, the intent-to-treat population). A secondary analysis for those patients who have completed the assessments at Weeks 4, 8, and 12 will also be performed.

During this study, safety will be evaluated based on the adverse events experienced by the patients. Efficacy will be evaluated primarily based on the following: (1) time to complete ulcer healing, (2) reduction of ulcer surface area, (3) resolution of rest pain, and (4) prevention of or reducing extent of amputation or other surgical interventions. Efficacy will also be examined by using the Rutherford Clinical Severity Score, and hemodynamic measurements (ankle-brachial index and great-to index).